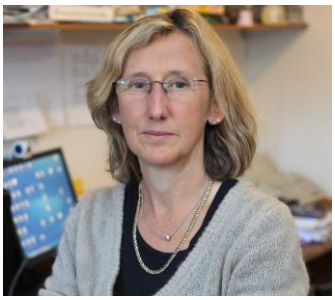
Use of Extended Irish Kindreds to Identify Novel ALS Variants

Acronym: ALSIBD



Principal Investigator: Orla Hardiman

Co Investigator: Dan Bradley

Grant: 98,000€

Project duration: 18 months

Summary of the research project

The genetic causes for the majority of ALS cases remain unexplained. A large number of genes have been implicated in the disease; each of these, however, only accounts for a small proportion of cases. It is likely that there are still numerous genes to be discovered that contribute to ALS and identification of these is vital to work out the causes of the disease, and to develop more effective treatments. As technological capabilities increase, identifying the entire genetic code for an individual is an exciting avenue in the discovery of new disease-causing genes. However, careful selection of informative individuals for analysis of the entire genetic sequence is essential to maximize the benefits of the findings. Distantly-related individuals from extended families are ideal in such studies; however, finding large families affected by ALS is difficult.

Dr.McLaughlin, a post doctoral researcher in our group has developed methodologies to discover distant shared ancestry amongst individuals with apparently sporadic ALS who were previously assumed to be unrelated. In the proposed project we will apply these methods to large Irish and UK datasets to infer distant relationships amongst ALS patients who do not have a family history of the disease. A small number of individuals will be carefully selected based on this information, and their entire genetic code will be sequenced to identify new disease-causing mutations. This will be useful in our future understanding of the causes of ALS and will help to understand the reasons for differences in the way the disease manifests in those affected.

Dr Russey McLaughlin

There is now evolving evidence that ALS is a syndrome rather than a single disease entity. Deep phenotyping and family aggregation studies indicate that disease subcategorization is both feasible and clinically relevant. This family history /phenotype/ genotype correlative research will provide new insights into mechanisms of disease pathogenesis, and will extend our knowledge of the interface between familial and sporadic forms of the disease. These findings will in turn be of benefit in clinical trial stratification.

The proposed work will be carried out in the Population Genetics Laboratory in the Smurfit Institute of Genetics (Dr.McLaughlin, Prof.Bradley), Trinity College Dublin. The bioinformatic techniques for

analysis of IBD in genome-wide SNP datasets will also be carried out by Dr.McLaughlin on UK and ALS cohorts in collaboration with Professor Al-Chalabi of King's College London

Professor Orla Hardiman is Professor of Neurology and Head of the Academic Unit of Neurology. Trinity Biomedical Sciences Institute, Trinity College Dublin, and Consultant Neurologist at the National Neuroscience Center of Ireland at Beaumont Hospital in Dublin (Ireland). She is a Fellow of the Royal College of Physicians of Ireland and Fellow of the American Academy of Neurology.

Dr.McLaughlin is a post-doctoral researcher jointly in Prof. Hardiman's and Prof.Bradley's (Population Genetics) laboratories.

Trinity Biomedical Sciences Institute

Pr Hardiman's five recent publications relevant to this research:

Kenna KP, McLaughlin RL, Byrne S, Elamin M, Heverin M, Kenny EM, Cormican P, Morris DW, Donaghy CG, Bradley DG, Hardiman O. Delineating the genetic heterogeneity of ALS using targeted high-throughput sequencing.
J Med Genet. 2013 Jul 23. doi: 10.1136/jmedgenet-2013-101795. [Epub ahead of print] PubMed PMID: 23881933.

Byrne S, Heverin M, Elamin M, Bede P, Lynch C, Kenna K, Maclaughlin R, Walsh C, Al Chalabi A, Hardiman O. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: A Population-Based Case-Control Cohort Study of Familial and Sporadic Amyotrophic Lateral Sclerosis.
Ann Neurol. 2013 Jul 9. doi: 10.1002/ana.23969. [Epub ahead of print] PubMed PMID: 23836460.

Kenna KP, McLaughlin RL, Hardiman O, Bradley DG. Using reference databases of genetic variation to evaluate the potential pathogenicity of candidate disease variants.
Hum Mutat. 2013 Jun;34(6):836-41. doi: 10.1002/humu.22303. Epub 2013. Mar 26. PubMed PMID: 23447461.

Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, Ince PG, Lin C, Miller RG, Mitsumoto H, Nicholson G, Ravits J, Shaw PJ, Swash M, Talbot K, Traynor BJ, Van den Berg LH, Veldink JH, Vucic S, Kiernan MC. Controversies and priorities in amyotrophic lateral sclerosis.
Lancet Neurol. 2013 Mar;12(3):310-22. doi: 10.1016/S1474-4422(13)70036-X. Review. PubMed PMID: 23415570.

Cronin S, Blauw HM, Veldink JH, van Es MA, Ophoff RA, Bradley DG, van den Berg LH, **Hardiman O**. Analysis of genome-wide copy number variation in Irish and Dutch ALS populations.
Hum Mol Genet. 2008 Nov 1;17(21):3392-8. doi:10.1093/hmg/ddn233.